

REMARKS

Claims 1 – 24 are pending in the application.

Rejection pursuant to 35 U.S.C. § 103

Claims 1 – 24 stand rejected under 35 U.S.C. § 103 as *prima facie* obvious over Chu, et al., Infection and Immunity, 40:245-56 (1983) (hereinafter "Chu et al.") in combination with Merck & Co. Inc., European Patent Application No. 0 497 525 A (hereinafter "EPA 0 497 525").

With regard to claims 1 – 12 and 14, the Examiner asserts that it would have been *prima facie* obvious to one of ordinary skill in the art to modify the conjugates of Chu et al. by combining any of the Pn-Ps-PRO of EPA 0 497 525 to provide for a vaccine containing up to ten different Pn-Ps-PRO conjugates. The Applicant respectfully disagrees.

To establish a case of *prima facie* obviousness, the Examiner must show, *inter alia*, a motivation to combine the references. The Applicant respectfully disagrees that either Chu et al. or EP 0 497 525, alone or in combination, suggest or provide any motivation to combine their teachings to arrive at the presently claimed invention. An aspect of the presently claimed invention is the use of at least two different protein carriers to avoid negative interference, the phenomenon whereby increasing concentrations of carrier protein lead to decreased immune response to the polysaccharide. As stated in the specification at p. 4, lines 12-18, "In order to overcome the problem which the phenomenon of negative interference constitutes in multivalent vaccines composed of polysaccharide conjugates, the present application proposes to use not one but at least two carrier proteins so that the maximum load of each of the carrier proteins is not reached." "Thus...a composition according to the invention should use at least two carrier proteins." See specification at p.6, lines 21-23, and at p.7, lines 7-14. The claims therefore recite compositions of *S. pneumoniae* polysaccharide conjugates comprising at least two carrier proteins that are different (*m* is > 1, viz. claim 1(d)), and that each conjugate comprise at least two carrier proteins that are different (viz. claim 1(e)).

There is no indication that Chu et al. contemplates negative interference. Chu's teaching is entirely lacking in any suggestion of control or avoidance of maximum carrier dose or, consequently, a way to avoid it. To the extent that Chu et al. used two different carrier proteins, there was no recognition

of any beneficial effect in using two carrier proteins that are different in a composition of conjugates, let alone in a composition of conjugates comprising *Streptococcus pneumoniae* polysaccharides.

Similarly, EP 0 497 525 does not provide any teaching of eliminating the negative interference of a multi-valent vaccine by using at least two protein carriers that are different. While EP 0 497 525 teaches vaccines comprising a mixture of one to ten different *pneumococcal* polysaccharide-immunogenic protein conjugates (Pn-Ps-PRO) that induce a broadly protective recipient immune response, and that the protein (PRO) portion of the conjugate may be an immune enhancer such as Tt or Dt, it does not teach the use of two or more different protein carriers in a single conjugate composition. EP 0 497 525 teaches the use of multiple *pneumococcal* polysaccharides in a composition comprising conjugates of the polysaccharides; EP 0 497 525 does not teach or suggest the use of multiple carrier proteins in such a composition.

The Examiner's presumption regarding the motivation to combine the references neglects the essential fact that vaccines are administered to healthy people. Adding a further component (in the present case, a second carrier) to a vaccinal composition known to be immunogenic, and therefore useful, is not obvious because the result is in itself unpredictable. Accordingly, there is hesitancy (rather than a motivation) to administer more than is necessary to a healthy person for fear encountering unexpected adverse consequences. One would not combine antigens unless there is a reasonable expectation of success. And in the field of immunology it is recognized that a combination of antigens does not necessarily result in a cumulative (let alone synergistic) response. Because of the phenomenon of antigenic competition, whereby a combination of antigens results in a decreased immune response, one could not have a reasonable expectation of success. Neither Chu nor EPA 0 497 525 suggests or motivates the use of at least two protein carriers. Neither teach or suggest an advantage of combining them or altering the compositions disclosed therein any way; the compositions of Chu et al and Merck & Co are already useful by themselves, as they are. In view of the hesitancy to add additional components and the uncertainty of the result of doing so, the requisite motivation and reasonable expectation of success are absent.

The Office Action argues that the motivation to combine references need not be the same in the prior art as in the claimed invention. But as neither Chu et al. nor EP 0 497 525 suggests it would be desirable to use multiple protein carriers in a composition comprising conjugates the Office's argument is irrelevant. In summary, neither Chu et al. nor EP 0 497 525 suggest or motivate the use

of at least two protein carriers in a composition of conjugates. Without such a suggestion or motivation, a *prima facie* case of obviousness cannot be established. Accordingly, the Applicant requests that the rejection of claims 1 – 12 and 14 be withdrawn.

With regard to claims 16, 17, 18 and 21, the Examiner asserts that it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the protein Dt as shown in EP 0 497 525 in the Hib-HCH conjugate of Chu *et al.* because Chu *et al.* teaches that a "useful" carrier would be preferred for human use. Even assuming that Dt is a "useful" carrier, as discussed above, there is nothing in Chu *et al.* that provides the motivation for one of skill in the art to use Dt and Tt together as carriers. Thus, the Applicant requests that the rejection of claims 16, 17, 18 and 21 be withdrawn.

With regard to claims 1 – 24, the Office Action also states that It would have been *prima facie* obvious to one of ordinary skill in the art to modify the conjugate composition of Chu *et al.* by adding any of the Pn-Ps-PRO conjugates of EPA 0 497 525 to provide a conjugate vaccine containing up to 23 different Pn-Ps-PRO conjugates. However, as stated above, the suggestion or motivation in either of Chu *et al.* or EP 0 497 525 to make this combination is simply absent. Thus, the Applicant requests that this rejection be withdrawn.

CONCLUSION


With the above amendments and remarks, the Applicant respectfully submits that the application is in condition for allowance. If the Examiner is of the opinion that a telephone conference would expedite prosecution of this matter, the Examiner is encouraged to contact the Applicant's undersigned representative.

Respectfully submitted,

McDonnell Boehnen Hulbert & Berghoff

Dated: April 19, 2004

300 South Wacker Drive
Chicago, Illinois 60606
312-913-0001


Michael Greenfield
Reg. No. 37,142